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Consequences of the Widespread Use of Antibiotics

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• *Great quantities of antibiotics are used each year. A direct result has been the appearance of large numbers of infections caused by organisms that are resistant to the action of one or more of these drugs. A new syndrome, that of superinfection by bacteria resistant to an antibiotic being administered, has become common. Its recognition is of great importance.*

The control of resistant infections requires the development of new antimicrobial agents and new knowledge about the use of older ones in combination.

The medical profession must be circumspect in its use of these important drugs or the time may come when the control of many serious infections may become impossible.

PHYSICIANS, to a greater extent than any persons, know of the impact of antimicrobial therapy on the practice of medicine and the natural history of infectious disease. Even they are not fully aware of the enormous quantities of these agents that are used in the United States each year. Penicillin is now being manufactured at a rate of well over 300 tons per annum—equivalent to 150 million courses of 3 million units each year. More than 100 tons of streptomycin are made, which would permit the administration of 100 million 1-gram doses of this agent.[8] The broad spectrum drugs are also produced in enormous quantities. It is believed that the rate is not less than 250 tons per annum. This is enough to permit the administration of 25 million 10-gram courses each year. Information is not readily obtained as to the production of the other less widely used antimicrobial agents, but it is substantial. Exact figures are not available but it may be readily calculated that more than half a billion dollars a year is spent by patients for these drugs. It is apparent, from these data, that few Americans can escape treatment with antibiotics for any length of time.

It is proper to inquire into the effects of this extraordinarily widespread use of biologically highly active chemical substances. The most important and readily demonstrable outcome has been the selective elimination of the antibiotic-sensitive forms of many common pathogens and the emergence of resistant variants as causes of human disease. In 1943, 90 per cent of all strains of staphylococcus aureus were inhibited by a few tenths of a unit of penicillin per cubic centimeter. This situation still prevails in those parts of the world where few antibiotics are used.[3] At present, 50 to 90 per cent of all strains isolated in the clinical bacteriological laboratory are intensely resistant to the action of this antibiotic.[2] Evidence obtained by culture of the respiratory tract of nonhospitalized patients suggests that the "wild" staphylococci among the population at large are much less frequently penicillin-resistant than are those harbored in the noses and throats of hospital personnel.[7] As a direct result of this fact, staphylococcus infec-

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tions acquired by patients in hospitals, or by physicians and nurses, are quite universally penicillin-resistant.

Equally disturbing has been the development of intensely tetracycline-resistant staphylococci during the relatively brief period that oxytetracycline and chlortetracycline have been in clinical use.[6] Erythromycin was substituted for penicillin in the routine treatment of patients in a middlewestern hospital. Within five months 70 per cent of all staphylococci isolated from the upper respiratory tracts of workers in that institution were resistant to the action of that drug although all had been sensitive when the experiment began.[5] There can be no doubt that many infections were caused by these resistant organisms. It is evident that staphylococci are highly adaptable microorganisms and it will be fortunate indeed if antimicrobial therapy remains effective for any great length of time in treatment of infections caused by them. Spink recently reported[10] mortality rates in staphylococcus sepsis comparable to those that were observed before any form of antimicrobial therapy was available.

Very similar changes have been seen in the large family of Gram-negative bacilli, particularly among the coliform-aerobacter group. Some years ago a very high percentage of these organisms were sensitive to the action of streptomycin and tetracycline. Table 1 indicates the results obtained in a survey during 1950-1953 in the author's laboratory. It will be observed that various Gram-negative bacilli are irregularly inhibited by the various available agents. It may be calculated from this information that an effective antibiotic will be selected correctly only 50 per cent of the time on the basis of chance alone when Gram-negative bacilli otherwise unidentified are the cause of the disease. This emphasizes the importance of precise *in vitro* study of this group of organisms by satisfactory methods for determining the ability of antibiotics to inhibit the growth of the bacteria.

A second extremely important development, directly the result of the widespread use of antibiotics, has been the increasingly frequent occurrence of infection by organisms which were virtually unknown a few years ago as causes of disease. The present clinical importance of the various pigmented Gram-negative bacilli, of which the Pseudomonas group is the most important, is outstanding.[1, 9] These organisms, generally intensely resistant to most of or all the available agents, are now common causes of urinary and respiratory tract infection, particularly in antibiotic treated patients. Bacteremia, meningitis and empyema are also now commonplace.

A third interesting and, at times, extremely serious

TABLE 1.—*Sensitivity of Gram-negative bacilli to antibiotics*

Organisms	Per Cent Sensitive		
	Streptomycin	Oxytetracycline	Chloramphenicol
E. coli	65.3	76.5	76.0
Paracolon	43.9	51.2	58.6
Proteus	64.6	6.2	16.7
Pseudomonas	19.7	14.5	6.6

outgrowth of antimicrobial therapy has been the clinical problem known as superinfection. This term simply denotes the appearance of an infectious process caused by an organism different from that which was responsible for the initial infection for which the patient was brought under antimicrobial therapy. Such superinfections may occur in the same area as the original process or in a different one. The former is seen most frequently in relationship to the urinary tract and to the lung. The latter may occur in the bowel where staphylococcus and other forms of bacterial enteritis are common, in the lung, the meninges, the endocardium and other sites. The pathogenesis of such superinfection is believed to be as follows: The use of antibiotics (particularly those of the broad spectrum group) suppresses the normal flora of the body cavities and eliminates the bacteria that usually cause disease in the various areas of the body, and this paves the way for invasion by resistant organisms. Some kind of competition undoubtedly exists between the normal and the disease-producing bacteria, which probably is one of the protective mechanisms by which the body deals with organisms that reach potentially infectable areas.

Recognition of such superinfection is of the greatest importance. It tends to occur in specific situations, particularly in the presence of obstructive disease of the urinary tract or of structural disease of the lung, and in special kinds of people—notably diabetics, alcoholics, infants, the aged, and the otherwise chronically sick or injured. Clinical recognition of superinfection is not difficult if there is at first striking improvement for a few days after the beginning of antimicrobial therapy, then relapse. In such circumstances superinfection may be assumed to be present. In many instances, however, this important complication occurs without any intervening period of definite alteration for the better in the clinical course. For this reason superinfection must be always suspected in a patient with an infectious disease which does not respond to antimicrobial therapy in the predicted fashion.

The ultimate recognition of superinfection involves the appropriate bacteriological study of blood, urine, sputum and other infected exudates. Unfortunately such techniques are not always available to practicing physicians. If they are not, the diagnosis must be made clinically. In any case in which antibiotics

are given for 72 to 96 hours without definite improvement, superinfection must be strongly suspected. Almost always in such cases, if appropriate bacteriological investigation cannot be carried out it is better to change to another drug, since if superinfection is present it is always resistant to the action of the antibiotic that is already being administered.

The final important effect of the widespread use of antibiotics and the emergence of organisms resistant to their action, has been the stimulation of research on several fronts. On one front are the large commercial drug firms, who have constantly sought new antimicrobial agents which might be useful in the treatment of resistant infection. Outstanding examples are bacitracin and erythromycin, introduced primarily for the treatment of resistant staphylococcal disease, and polymyxin, whose principal role is in the treatment of Pseudomonas infection. A second important development has been a keen interest in the potential role of combined antibiotics in the treatment of disease.[4] Lastly, it has been necessary to reevaluate methods and techniques. The medical profession is rapidly becoming aware that it must discriminate in the use of antibiotic drugs so that these valuable chemicals will not be wasted in the treatment of trivial disease or in needless prophylaxis, lest the time arise when they will not be available as life-saving agents in patients with serious infections.

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